REMARKS

Amendments to the specification

The title and abstract have been amended to correspond to the pending claims.

The Brief Description of the Drawings at Figure 13 has been amended to include the appropriate sequence identifiers.

The sequence listing has been amended to reflect the correct inventorship.

No new matter has been added.

Amendments to the claims

Claims 27-35, 38, 39, 42-46 and 49-51 are pending. Claims 42-46 are withdrawn from examination. Applicants appreciate the Examiner's acknowledgement that claim 31 is allowable.

Claims 27, 31, 32 and 33 have has been amended.

Claims 27, 31 and 33 have been amended to provide appropriate punctuation.

Claim 32 has been amended to depend from both claim 27 and claim 31.

New claims 53-56 have been added. New claims 53 and 54 further define the melanoma antigen of claim 32. Support for these claims can be found throughout the specification as originally filed, *e.g.*, at page 5, lines 3-9; page 5, line 36 through page 6, line 2; page 39 and lines 1-17.

New claims 55 and 56 are drawn to a composition comprising the molecular conjugates of claims 53 and 54. Support for these claims can be found throughout the specification as originally filed, *e.g.*, at page 2, lines 8-11; page 5, lines 3-9; page 5, line 36 through page 6, line 2; page 6, lines 7-18; and page 39 and lines 1-17.

No new matter has been added by way of the foregoing amendments, which have been made solely to expedite prosecution and in no way should be viewed as acquiescence to any rejection. Applicants reserve the right to pursue the claims as originally filed in this or subsequent applications.

Drawings

With regard to the Examiner's objection to Figure 13 as not including sequence identifiers, Applicants respectfully refer the Examiner to substitute Figure 13 included with Applicants' response filed on July 24, 2004. Substitute Figure 13 includes the appropriate

sequence identifiers. For the Examiner's convenience, a copy of substitute Figure 13, as filed on July 24, 2004, is enclosed herewith. As noted above, the brief description of Figure 13 (at page 8) has been amended to include these sequence identifiers. Accordingly, this objection is moot.

Priority

Priority to application no. 09/851614 is denied because the currently pending claims do not recite that the human antibodies are "specific" for dendritic cells "as recited in claims 1 and 5" of the '614 application. Applicants respectfully disagree.

From the outset, Applicants respectfully note that the claims of the parent '614 application are not the only basis for determining whether the presently pending claims are entitled to priority to the '614 application. Instead, the teachings of the entire '614 specification should be considered. In this regard, the priority application, 09/851614 teaches that "[t]he phrases 'an antibody recognizing an antigen' and 'an antibody specific for an antigen' are used interchangeably herein with the term 'an antibody which binds specifically to an antigen'" (see, *e.g.*, page 13, line 37 through page 14, line 2). Moreover, antibodies which "bind" to dendritic cells, without reference to "specific" binding, are described throughout the parent '614 application (for example, at page 2, lines 20-24, and page 9, lines 29-31). Accordingly, the presently claimed human antibodies which "bind" to dendritic cells are clearly supported in the prior '614 application and Applicants are entitled to their priority claim.

Priority to the '614 application is also denied because the currently pending claims do not recite that the human antibodies have the following characteristics, as recited in claim 1 of the parent '614 application:

a) a binding affinity constant to a dendritic cell of at least about 10^7 M^{-1};

b) the ability to opsonize a dendritic cell;

c) the ability to internalize after binding to dendritic cells; or

d) the ability to activate dendritic cells.

Applicants respectfully disagree. Again, the entire specification, not just the claims of the priority application, provides the basis for determining priority. Support for the presently claimed antibodies which are defined by their ability to bind dendritic cells and/or by sequence are taught throughout the parent '614 application, for example, at page 2, lines 8-

18, page 62 and line 20 through page 63, line 10. As stated in the parent '614 application, for example, at page 3, lines 1-20 and page 22, line 20 through page 23, line 14, various embodiments of the invention include human antibodies which bind dendritic cells and which may/or may not have various functional properties, such as the properties recited above, as well as other properties taught in the '614 application.

Specifically, support for claim 27, drawn to a molecular conjugate comprising a human monoclonal antibody that binds to the human macrophage mannose receptor, linked to an antigen, such as a pathogen, a tumor antigen, an autoantigen, a melanoma antigen or Pmel-17 (claims 28, 29, 31, 32, 53 and 54), can be found, *e.g.*, at page 5, lines 1-4, of the parent '614 specification. Support for the antibody fragments or single chain forms of the claimed antibodies (claim 30) can be found, for example, at page 2, lines 24-28 of the parent '614 specification. Support for molecular conjugates comprising anti-dendritic cell antibodies having the claimed heavy and light chain variable region sequences (claims 31 and 34) can be found, *e.g.*, in Figure 9 of the parent '614 specification. The currently claimed molecular conjugate encoded by SEQ ID NO:8 (claim 35) is also described in the parent '614 specification, for example, in Figure 13. Support for the currently claimed compositions comprising the molecular conjugates of the present invention (claims 38, 39, 55, and 56) can be found throughout the parent '614 specification, *e.g.*, at page 6, lines 28-31. Support for the currently claimed molecular conjugates which bind to the human mannose receptor having SEQ ID NO:7 (claim 51) can also be found in the parent '614 specification, for example, at page 64, lines 18-20. The claimed molecular conjugates which are produced as a recombinant fusion protein or chemical conjugate (claim 52) are described in the parent '614 specification, *e.g.*, at page 4, lines 26-32. Accordingly, the presently claimed human antibodies are clearly supported by the parent '614 application and Applicants are entitled to their priority claim.

Rejection of Claims 27-30, 32, 33, 35, 38, 39, and 50-52 Under 35 U.S.C. §103(a)

Claims 27-30, 32, 33, 38, 39, and 50-52 are rejected as being unpatentable over U.S. Patent No. 5,922,845 in view of Tuting *et al.* (1998) and Sallusto *et al.* (1995).

Applicants respectfully traverse this rejection. The Examiner's rejection incorrectly assumes that all known receptors on dendritic cells were believed suitable for antibody-mediated antigen targeting, at the time of the present invention, as had been shown in the

'845 patent for Fc receptors. However, this was clearly not the case, particularly for the macrophage mannose receptor. As discussed in detail in the accompanying Declaration by Dr. Tibor Keler, there were, in fact, several reasons why one of ordinary skill in the art would not have believed the macrophage mannose receptor to be suitable for antibody-based vaccines, including what was known about the mechanism of antigen uptake and processing employed by this receptor. Therefore, there would not have been the requisite motivation at the time the application was filed to have linked a human anti-mannose receptor antibody to an antigen.

Briefly (and with reference to the accompanying Declaration by Dr. Keler), monoclonal antibodies were known in the art to bind target epitopes (*e.g.*, target receptors) with affinities far greater than the carbohydrate interactions between mannosylated antigens and the mannose receptor. This level of binding would not have been thought suitable for targeting antigens to the mannose receptor, since it would have been expected that the antibody – antigen conjugate would fail to dissociate from the receptor once internalized. Indeed, antibodies which bind the human mannose receptor would not have been expected to exhibit the specialized multivalent properties of mannose receptor ligands necessary for antigen presentation, *i.e*, such antibodies would not have been expected to exhibit low affinity interactions capable of efficient dissociation of the ligands and antigens in the intracellular compartments. Furthermore, antibodies to the mannose receptor had been shown to block antigen uptake as described by Sallusto *et al.* (1995), suggesting that this approach may interfere with internalization or receptor multimerization.

With respect to the Examiner's contention that one of ordinary skill "would have simply selected an antibody with reduced binding affinity . . .," Applicants respectfully disagree. There is no evidence in the art to suggest that low affinity antibodies would allow for efficient binding to cellular targets in tissues such as lymph nodes. Antibodies with moderate to good binding affinity would still have higher affinity than most carbohydrate based interactions, as the latter are generally efficiently blocked using antibodies specific for the receptor.

Therefore, there was no motivation or reasonable expectation of success at the time of Applicants' filing to have tried using antibodies directed to the mannose receptor to target antigens to dendritic cells for efficient antigen uptake and presentation, or for any other purpose whatsoever. Indeed, this is evidenced by the fact that mannose-mediated uptake of

antigens had been known since the early 1990's, yet no one in the art had tried using antibodies directed to the mannose receptor, in place of mannose receptor ligands, to mediate uptake of antigens. If it was obvious to have done so, then the prior art would have tried it. The prior art did not. Indeed, Applicants were the first to use antibodies which bind the human mannose receptor to target antigens to the receptor.

Moreover, as further described in the accompanying Declaration and confirmed by Sallusto *et al.*, there is a clear distinction between mannose receptor-mediated endocytosis of ligands and Fc receptor-mediated internalization ligands, the latter of which results in delivery to lysozomes and the degradation of both the ligand and the receptor. Accordingly, one of ordinary skill would not have been motivated to have used antibodies to target antigens to dendritic cells via the mannose receptor, since such antibodies would have been expected to also inherently bind to the Fc receptors expressed on these cells via their constant regions, regardless of what receptor they were targeting. Such binding would have lead to degradation of the antibodies rather than presentation by, for example, the mannose receptor. Additional mechanisms for capturing antigens, like macropinocytosis, are also far different from antibody-mediated antigen presentation, and would not have been thought suitable for antibody-based vaccines.

Indeed, prior to the present invention, the mannose receptor was not recognized to capture and process antigens via antibodies. In fact, the anti-mannose receptor antibodies developed by Applicants as part of the present invention were initially selected by Applicants based on their superior functional properties (*e.g.*, efficient internalization and antigen presentation) before it was known what specific receptor on dendritic cells the antibodies bound to. It was entirely unexpected when the antibodies were later characterized as binding to the human mannose receptor. Moreover, the antibody-mediated internalization observed by Applicants using the presently claimed anti-mannose receptor antibodies was found to involve mechanisms which were entirely different and independent of those involved in model mannose receptor ligand internalization as described in Ramakrishna *et al.* (2004) J. Immunol. 2846-2852, authored by the inventors of the present application and colleagues who did not provide inventive contribution to the currently pending claims.

The Examiner comments that Ramakrishna *et al.* "do not indicate anything unexpected, surprising, nor particularly difficult in producing a functional conjugate." However, Applicants respectfully note that a *prima facie* case of obviousness requires

motivation to have made the claimed invention in the first place. The fact that, after Applicants conceived of the invention, they made it without difficulty does not cut against the fact that it was not obvious to have made the invention from the start. Indeed, it is improper to rely on hindsight to establish obviousness.

Moreover, with respect to dependent claims 28-30, 32, 33 and 35, the prior art did not teach or suggest targeting the particularly claimed antigens to the mannose receptor via antibodies (see, claims 28, 29, 32, and 33), or using antibody fragments or single chain antibodies (see, claim 30), let alone the specific molecular conjugate encoded by SEQ ID NO:8 (claim 35).

Accordingly, because at the time of the present invention it was understood that antigens were presented via the mannose receptor by mechanisms which greatly differed from antibody-targeted mechanisms and would not have been thought suitable for developing antibody-based vaccines, there would not have been sufficient motivation to have made the presently claimed molecular conjugates comprising a human monoclonal antibody that binds to the human macrophage mannose receptor linked to an antigen. Importantly, it was not until Applicants' invention that antibodies to the human macrophage mannose receptor were unexpectedly discovered to be useful for antigen presentation. Therefore, the presently claimed invention would not have been obvious and Applicants respectfully request withdrawal of the present rejection.

Rejection of Claims 27-30, 32, 33, 38, 39 and 50-52 Under 35 U.S.C. §103(a)

Claims 27-30, 32, 33, 38, 39, and 50-52 are rejected as being unpatentable over U.S. Patent Application Publication No. 2002/0187131 in view of U.S. Patent No. 5,922,845 and Tuting *et al.* (1998).

Applicants respectfully traverse this rejection. The '131 application is directed to the DEC-205 receptor, not the mannose receptor as presently claimed. Again, the Examiner incorrectly assumes that all receptors on dendritic cells were believed equally suitable for antibody-based vaccines. Like Fc receptors, the DEC-205 receptor was known to be functionally very different from the macrophage mannose receptor. Importantly, for the reasons discussed above in the accompanying declaration, the substance of which is reiterated here, one of ordinary skill in the art at the time the present application was filed would not, in contrast to Fc receptors and DEC-205, have thought the mannose receptor suitable for

antibody-based vaccines. It was not until Applicants' invention that antibodies to the human macrophage mannose receptor were unexpectedly discovered to be useful for antigen presentation. Therefore, the presently claimed invention would not have been obvious and Applicants respectfully request withdrawal of the present rejection.

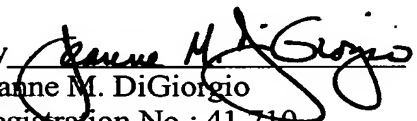
SUMMARY

In view of the foregoing amendments and arguments, reconsideration and withdrawal of all the rejections and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call (617) 227-7400.

Applicants believe no additional fee is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 12-0080, under Order No. CDJ-166CPRCE from which the undersigned is authorized to draw.

Dated: November 22, 2006

Respectfully submitted,

By 

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